PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 501731/MRO/mro	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. PCT/AU2003/001166	International Filing Date *(day/month/year)* 5 September 2003	Priority Date *(day/month/year)* 5 September 2002

International Patent Classification (IPC) or national classification and IPC

Int. Cl. [7] C12Q 1/68; G01N 33/53

Applicant

GARVAN INSTITUTE OF MEDICAL RESEARCH et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheet(s).

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☒	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

Date of submission of the demand	Date of completion of the report
26 March 2004	21 December 2004
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **TERRY MOORE** Telephone No. (02) 6283 2632

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU2003/001166

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed.

[ ] the description, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages , received on with the letter of

[ ] the drawings, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/fig.

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU2003/001166

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be nonobvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos: 6, 8, 13, 14, 21, 23, 28, 29, 44, 46, 54-59 and 70-73 in full and 1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 50-53, 60-69 in part .

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claim Nos. 6, 8, 13, 14, 21, 23, 28, 29, 44, 46, 54-59 and 70-73 in full and 1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 50-53, 60-69 in part . (See unity, observations and supplemental boxes)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU2003/001166

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 15 and 30 in full and 1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47-53 and 60-69 in part. (see supplemental box 2, particularly note about claims 9 and 24)

V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims **45 and 47-53**	**YES**
	Claims **1-5, 7, 10-12, 15-17, 18-20, 22, 25-27, 30-43 and 60-69**	**NO**
Inventive step (IS)	Claims **45 and 47-53**	**YES**
	Claims **1-5, 7, 10-12, 15-17, 18-20, 22, 25-27, 30-43 and 60-69**	**NO**
Industrial applicability (IA)	Claims **1-5, 7, 10-12, 15, 17, 18-20, 22, 25-27, 31-43, 45, 47-53 and 60-69**	**YES**

2. Citations and explanations (Rule 70.7)

The invention relates to the use of specific nucleic acid and peptide sequences in methods of detecting, treating and characterising ovarian cancers.
The following documents identified in the International Search Report have been considered for the purposes of this report:

D1 DGENE Abstract ABS76418
D2 WO 2002 071928
D3 DGENE Abstract AAZ77553
D4 WO 1999 053040
D5 WO 2003 068054
D6 WO 2002 102235
D7 WO 2001 094629
D8 DGENE Abstract ABL62031
D9 DGENE Abstract ABL67667
D10 DGENE Abstract ABL61830
D11 Hough et al (2000) Cancer Research

D2 and its related DGENE abstract D1, D5 and D6 are all patent documents published after the priority date of the current application and they may be relevant to the novelty of the claims during national phase examination. They are discussed in the following section "Certain documents cited".

Novelty and Inventive Step

D3 discloses galactin 4 (SEQ ID NO 57) and its use as a marker for the detection, diagnosis and treatment of ovarian cancer. D3 also discloses use of galactin 4 to identify agents suitable for the treatment of ovarian cancer. As such the citation is relevant to the novelty and inventive step of claims 1-5, 10, 11, 15, 16-20, 22, 25, 26, 31-43 and 60-69.

However D3 does not disclose the markers of claims 45 and 47-53 or the specific ovarian cancers of claims 12 and 27. Therefore, it appears that these claims are novel and inventive in light of D3.

Continued in supplemental box 1.

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
WO 2002 071928 (D2)	19-09-02	14-03-02	14-03-01
WO 2003 068054 (D5)	21-08-03	13-02-03	13-02-02
WO 2002 102235 (D6)	27-12-02	18-06-02	18-06-01

D2 discloses the use of sox17 (SEQ ID 17) as a marker in assays for the diagnosis and prediction of ovarian cancer and for the identification of drugs for treating of ovarian cancers. It also discusses using markers to determine metastasis, and to indicate a patient's likelihood of survival or recovery. As such D2 is relevant to the novelty of claims 1-5, 7, 10, 11, 16-20, 22, 25, 26, 31-43 and 60-69.

D5 discloses sFRP4 (SEQ ID 69) on page 33/60 and as SEQ ID NOS 515-517 and discusses the sequences as a marker for ovarian cancer and to identify agents for treating and monitoring of ovarian cancer. The marker is used in nucleic acid and immuno assays and to follow progression of the cancer. As such the citation is relevant to the novelty of claims 1-5, 7, 10, 11, 16-20, 25, 26, 31-43 and 60-69.

D6 discloses "STAT induced STAT inhibitor 3" at page 125, which appears to be a synonym for SOCS 3 (SEQ ID NO 73, 74). The citation the detection and diagnosis of ovarian cancer and the identification of agents useful in the treatment of ovarian cancer. As such the citation is relevant to the novelty of claims 1-5, 7, 10, 11, 16-18-20, 25, 26, 31-43 and 60-69.

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 48-50 do not appear to be fully supported by the description. There is nothing in the description to suggest how detection of SOCS 3 or sFRP4 markers can be used to determine the likelihood of survival from ovarian cancer. Although the specification discloses use of these markers to detect the cancer and to assess the progression of the cancer, there is nothing to suggest how these methods might be modified to determine the likelihood of survival or how these markers may be indicative of a high or low likelihood of survival. The only clear reference to markers used in this way is at table 4; however this relates to SOX17, CLDN3, Ep-CAM, CA125, MUC1 and E cadherin, not SOCS 3.

Claims 70-73 are not fully supported by the description. The claims recite methods of detecting aberrant methylation in the promoter of a gene associated with ovarian cancer, however the specification does not disclose any promoters. All of the sequences disclosed in the specification are transcribed sequences and as such they do not include promoters. As such, the specification does not provide sufficient information for the skilled person to carry out the claimed methods as a matter of routine.

Supplemental Box 1
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box V

D7 discloses methods of treating and diagnosing cancer using the L1 cadherin (SEQ ID NO 6004), meprin A (SEQ ID NO 167) and Socs 3 (SEQ ID NO 368) markers. D7 is associated with D8-D10, which represent the 3 DGENE accessions associated with SOCS 3, L1 cadherin and meprin A respectively, the applicant's SEQ ID NOS 59-62, 73 and 74. D7 identifies a restricted range of cancers, including ovarian, where these markers are elevated. The citation also discloses testing these genes as agents for the treatment of cancer and using the presence of these markers as an indicator of the continued presence or progression of the cancer. As such, D7 is relevant to the novelty and inventive step of claims 1-5, 7, 10, 11, 15-20, 22, 25, 26, 30-43 and 60-69.

However D7 does not disclose the markers of claims 45 and 47-53 or the specific ovarian cancers of claims 12 and 27. Therefore, it appears that these claims are novel and inventive in light of D7.

D11 discloses claudin 3 (SEQ ID NO 15) as a marker for ovarian cancer. In particular the citation assesses claudin 3 expression levels in serous and epithelial ovarian cancers. Both nucleic acid and immuno assays are disclosed. As such the citation deprives claims 1-5, 7, 10-12, 16-20, 25-27, 31-34 and 66-69 of novelty and inventive step. Furthermore, although the citation does not disclose the assay devices and chips claimed in claims 60-65, it is standard practice in the art to use markers of interest on gene-assay chips, as such claims 60-65 lack an inventive step in light of D11.

However, D11 does not disclose the markers of claims 45 and 47-53 or methods of identifying agents for the treatment of ovarian cancer as defined in claims 66-69. As such, it appears that these claims are novel and inventive in light of D7.

Supplemental Box 2
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Supplemental Box 1 (Novelty and Inventive Step)

D7 discloses methods of treating and diagnosing cancer using the L1 cadherin (SEQ ID NO 6004), meprin A (SEQ ID NO 167) and Socs 3 (SEQ ID NO 368) markers. D7 is associated with D8-D10, which represent the 3 DGENE accessions associated with SOCS 3, L1 cadherin and meprin A respectively, the applicant's SEQ ID NOS 59-62, 73 and 74. D7 identifies a restricted range of cancers, including ovarian, where these markers are elevated. The citation also discloses testing these genes as agents for the treatment of cancer and using the presence of these markers as an indicator of the continued presence or progression of the cancer. As such, D7 is relevant to the novelty and inventive step of claims 1-5, 7, 10, 11, 15-20, 22, 25, 26, 30-43 and 60-69.

However D7 does not disclose the markers of claims 45 and 47-53 or the specific ovarian cancers of claims 12 and 27. Therefore, it appears that these claims are novel and inventive in light of D7.

D11 discloses claudin 3 (SEQ ID NO 15) as a marker for ovarian cancer. In particular the citation assesses claudin 3 expression levels in serous and epithelial ovarian cancers. Both nucleic acid and immuno assays are disclosed. As such the citation deprives claims 1-5, 7, 10-12, 16-20, 25-27, 31-34 and 66-69 of novelty and inventive step. Furthermore, although the citation does not disclose the assay devices and chips claimed in claims 60-65, it is standard practice in the art to use markers of interest on gene-assay chips, as such claims 60-65 lack an inventive step in light of D11.

However, D11 does not disclose the markers of claims 45 and 47-53 or methods of identifying agents for the treatment of ovarian cancer as defined in claims 66-69. As such, it appears that these claims are novel and inventive in light of D7.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of IV (unity)

The application claims more than one invention. Rule 13.1 of the PCT states the principle that an International Application should relate to only one invention or, if there is more than one invention, that the inclusion of those inventions in one International Application is only permitted if all inventions are so linked as to form a single general inventive concept.

Rule 13.2 of the PCT defines the method for determining whether the requirement of unity of invention is satisfied in respect of a group of inventions claimed in an International application. Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features." The expression "special technical features", is defined in Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. The determination is made on the contents of the claims as interpreted in light of the description and drawings (if any).

The claims and the description relate to methods for the diagnosis, prediction and treatment of ovarian cancer, using gene and peptide sequences whose expression is altered in ovarian cancer. In particular the claims define methods relating to the use of over 693 specific gene and/or peptide sequences.

Although all of the claims share the common feature that they all relate to methods or apparatus that involve the use of specific gene or peptide sequences whose expression is altered in ovarian cancer, this feature is known (see the documents listed below). As such this feature cannot be regarded as a special technical feature and cannot confer unity on the inventions relating to the use of specific gene or peptide sequences for the detection or treatment of ovarian cancer.

D1 US 5 912 142
D2 US 6 268 165
D3 WO 01 21653
D4 Bayani et al (2002) Cancer Research 62, 3466-76

Furthermore, there is nothing in the specification to suggest that the genes can be further divided into groups, where sequences within a group share a common special technical feature. Although the specification discloses that some of the genes can be classified into further, narrower groups, these further divisions also cannot be regarded as special technical features. These divisions correspond to groups of genes that are down-regulated or up-regulated in cancers and genes that are associated with specific types of ovarian cancers, such as epithelial or mucinous ovarian cancer. However these groups are known, as are methods of using genes specifically associated with these narrower groups for the treatment and detection of specific subsets of ovarian cancers (See in particular D4). As such, there is no unity between the methods claimed as they relate to independent gene sequences.

At the ISR stage, on payment of four additional search fees, the ISA agreed to search methods relating to a total of 50 independent gene sequences. As such the ISR relates to the 50 sequences, SEQ ID NOS 1- 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 60- 63, 65, 67, 69, 71-75, 77, 79, 81, 83.

The IPEA issued an invitation to pay additional fees to cover the five inventions searched in the ISR. The applicant chose not to accept the invitation and nominated 10 sequences of the fifty sequences that were the subject of the ISR for examination at the IPE stage. These sequences were SEQ ID NOS 15, 17, 57, 59, 60, 61, 62, 69, 73 and 74. As such this IPEO is restricted to examination of these 10 sequences.

As a consequence claims 15 and 30 in full and 1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47-53 and 60-69 in part, are the subject of this opinion. Claims 9 and 24, which were searched in the ISR, are not the subject of this report because they relate to SEQ ID NOS 1-6, which were not among the SEQ ID NOS specified by the applicant.